DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IV, claims 16, 17, 19, 47-48, 92 and 98, drawn to a composition comprising a gastrin/CCk receptor ligand, and of specie glucagon-like peptide 1 receptor ligand, in the reply filed on 1/23/2008 is acknowledged.

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Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 16, 17, 19, 47-48, 92 and 98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a composition comprising a gastrin/CCK receptor ligand and a factor for complementing gastrin for islet neogenesis therapy (a FACGINT), provided that the FACGINT is not an EGF receptor ligand, or kit for treating or preventing diabetes, the kit comprising the composition mentioned above. Also at least one of the gastrin/CCK receptor ligand or the FACGINT may be formulated fro sustained release formulation. Thus, the claims are drawn to a composition that

contains a genus of FACGINT compounds. The specification , on page 2, discloses a list of FACGINT compounds which are related by just the property claimed (i.e., complementing gastrin for islet neogenesis therapy) but are from different families of ligands or growth factors that have their mode of action through a variety of unrelated signal transduction pathways. In this case the art has not established a strong correlation between structure and function, and therefore one skilled in the art would not be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing “a result that one might achieve if one made that invention”). Given the fact that there is no unifying partial structure of mode of action, correlating the claimed property to the structure, a person of ordinary skill in the art would not be able to determine other compounds that form the genus claimed.

An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of

Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)

Therefore, only the compounds listed in the specification as FACGINTs, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

4. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes, does not reasonably provide enablement for prevention of diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Specifically, the claim is drawn to a kit for treating or preventing diabetes, the kit comprising a composition comprising a gastrin/CCK receptor ligand and a factor for complementing gastrin for islet neogenesis therapy (a FACGINT), provided that the FACGINT is not an EGF receptor ligand.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation

needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification provides data enabling the use of the composition for treating diabetes in non-obese diabetic mice, including dosage and dosing regimens (Example 1), which is consistent with the findings in prior art. Regarding the prevention of diabetes, the standard for prevention is considerably higher than the use of the kit to treat the disease. The disease is supposed to be blocked from appearance altogether, a claim that is hard to sustain due to the multifactorial nature of such a complex disease as diabetes and the multiple form of manifestation such as juvenile diabetes, gestational diabetes, adult early onset diabetes, etc. All these aspects were not addressed in the specification and a person of ordinary skill in the art, while knowing to treat diabetes, would have no guidance as to prevent the apparition of diabetes. In the best case scenario, a skilled artisan would be able to use the guidance and the working examples to prevent the diabetes progression but not the appearance of the disease. In order to prevent the apparition of diabetes, a person of ordinary skill in the art would have to perform a huge amount of experimentation so as to consider all the factors that lead to the apparition of the disease and all the form of manifestation. This amount of experimentation is considered undue.

Due to the large quantity of experimentation necessary to test all the factors and multiple conditions that together lead to the apparition of diabetes; the absence of guidance and working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the complexity of the disease and the

unpredictability of all these factors, undue experimentation would be required of the skilled artisan to use the claimed invention in a manner commensurate with its full scope.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 17 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites "a dosage effective for inducing differentiation of...". Dosage is intended use. What the dosage is depends on the concentration in the tube, and how much it is administered. Therefore, the metes and bounds of the claim 17 could not be determined.

For claim 19 it is unclear if the composition in the container and what is the relationship between elements of the kit.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 16, 17, 19 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nardi et al. (U. S. Pat. 5,885,956- cited by Applicant) in view of Peck et al. (U. S. Pat. 6,001,647).

The claims are drawn to a composition comprising a gastrin/CCK receptor ligand and a factor for complementing gastrin for islet neogenesis therapy (a FACGINT), provided that the FACGINT is not an EGF receptor ligand, or kit for treating or

preventing diabetes, the kit comprising the composition mentioned above. Also at least one of the gastrin/CCK receptor ligand or the FACGINT may be formulated fro sustained release formulation.

Nardi et al. teach a composition comprising a gastrin/CCK receptor ligand, e.g. a gastrin, and an EGF receptor ligand, e.g. TGFα in an amount sufficient to effect differentiation of pancreatic islet precursor cells to mature insulin-secreting cells (abstract). The composition is used for treatment of diabetes mellitus by effecting the differentiation of pancreatic islet precursor cells into mature insulin-producing cells by the combined synergistic stimulation by a gastrin/cholecystokinin (CCK) receptor ligand, particularly gastrin, and an epidermal growth factor (EGF) receptor ligand, particularly transforming growth factor alpha (TGFα) (col.1, lines 5-13). Complete islet cell neogenesis was reactivated in vivo in mammals in the ductular epithelium of the adult pancreas by stimulation with a gastrin/CCK receptor ligand, such as gastrin, and an EGF receptor ligand, such as TGFα. Both types of growth factors are required to achieve the envisioned objective, neither one alone is sufficient. Regenerative differentiation of residual pluripotent pancreatic ductal cells into mature insulin-secreting cells has become a viable clinical option for the treatment of diabetes mellitus, particularly juvenile onset diabetes, by therapeutic administration of this combination of factors or compositions which provide for their in situ expression within the pancreas (col. 2, lines 21-39).The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder (col.6, lines 12-13).

Nardi et al. are silent about the use of other growth factors in combination with gastrin, which according to the state of the art cited by Nardi et al., was known to be associated with islet development (col.1, lines 45-64) and are also silent about addressing the issue of immune suppression

Peck et al. teach growth, propagation and differentiation of a pancreatic stem cell, i.e., a progenitor cell or cells that give rise to the formation of all of the different types of cells and tissue that make up a normal pancreas. Also taught is the in vivo use of in vitro grown pancreatic stem cells to produce pancreas-like structures or an "ecto-pancreas" organ that exhibits functional, morphological and histological characteristics similar to those observed in a normal pancreas. Thus, the ability to produce a functional "ecto-pancreas" in vivo from in vitro grown pancreatic cells can be used to treat, reverse or cure a wide variety of pancreatic diseases that are known to result in or from damage or destruction of the pancreas. The author also mention that In normal adult pancreas, approximately 0.01% of the cells within the ductal epithelium can be stimulated to undergo morphogenic changes to form new islets, reminiscent of neogenesis (col. 6, lines 20-46). This neogenesis has been induced experimentally by dietary treatment with soybean trypsin inhibitors or high levels of interferon-γ keratinocyte growth factor, fibroblast growth factor and other growth factors. One of the factors is hepatocyte growth factor/scatter factor which induces β cell proliferation resulting in increased mass. Thus, a population of precursor/stem cells remained in the adult pancreatic ducts and differentiation of this population can be evoked in vivo in response to specific stimuli (col. 8, line 42 to col. 9. line 22). Peck et al. also teach the genetic engineering of islet

cells to resist subsequent immunological destruction. For example, the cultured islet cells can be transformed to express a protein or peptide which will inhibit or prevent the destructive immune process. Other useful proteins or peptides may be expressed (col. 5, line 64 to col. 6 line 2) and thus address the need to minimize immune suppression.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to test other growth factors (as taught by Peck et al.) in combination with gastrin for a composition to be used for islet neogenesis therapy as taught by Nadir et al. with a reasonable expectation of success. That is because Nadir et al. proved that two factors, gastrin and TGFα gave unexpected results when combined. A person of ordinary skill in the art would have had to test a limited number of compounds from the list of Peck et al. to obtain a better combination. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

11. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nardi et al. (U. S. Pat. 5,885,956) in view of Perfetti et al. (Endocrinology, 141, 4600-4605, 2000- cited by Applicant).

The claim is drawn to a composition comprising a gastrin/CCK receptor ligand and a GLP-1 receptor ligand, for treating diabetes.

The considerations of Nardi et al. were presented supra. Nardi et al. does not specifically mention GLP-1 for being combined in a composition for treating diabetes.

Perfetti et al. teach that treatment of aging rats with GLP-1 induced β cell neogenesis and pancreatic cell proliferation (abstract). Also taught is the use of the GLP-1 for treating diabetes and especially Type 2 diabetes (discussion section).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to test GLP-1 (as taught by Peck et al.) in combination with gastrin for a composition to be used for islet neogenesis therapy as taught by Nadir et al. with a reasonable expectation of success. That is because Nadir et al. proved that two factors, gastrin and TGFα gave unexpected results when combined. A person of ordinary skill in the art would have had to test limited number of compounds (GLP-1 and analogs) to obtain a better combination. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

12. Claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nardi et al. (U. S. Pat. 5,885,956) in view of Perfetti et al. (Endocrinology, 141, 4600-4605, 2000-cited by Applicant) and in further view of Wunsch et al. (Hoppe-Seyler's Z. Physiol. Chem. 363, 665-669, 1982).

The claim is drawn to a composition comprising a gastrin/CCK receptor ligand and a GLP-1 receptor ligand, for treating diabetes, wherein the gastrin is gastrin I having 17 amino acids with a Leu residue at amino acid position 15.

The teachings of Nadir et al. and Perfetti et al. where presented supra. Neither of them contemplates the use of the M15L mutant of Gastrin I.

Wunsch et al. teach that the methionine at position 15 can be replaced by Leucine without loss of potency (Table 1 and p. 667, left col., second full paragraph). The reason for the substitution is to avoid possible deactivation resulting from oxidation of the methionine side chain to its sulfoxide derivate as observed to easily occur in the case of gastrin family via air oxidation (Introduction section).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to modify the Gastrin in the combination of the gastrin and GLP-1 as taught by Nadir et al. and Perfetti et al. and use the M15L mutant of Wunsch et al. with a reasonable expectation of success. That is because Wunsch et al. proved that there is no change in activity for the Gastrin I M15L mutant and the motivation was also offered by Wunsch et al. to obtain a more stable product to be used for therapy.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Fisk et al. (U. S. Pat. 7, 033,831). This disclosure provides a system for producing pancreatic islet cells from embryonic stem cells. Differentiation is initiated towards endoderm cells, and focused using reagents that promote emergence of islet precursors and mature insulin-secreting cells. High quality populations of islet cells can be produced in commercial quantities for use in research, drug screening, or regenerative medicine.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Lorraine Spector/ Ph.D.

Primary Examiner, Art Unit 1647

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